

The graphic features a purple rectangular background with a white border. The text "Microbicide Trials Network (MTN)" and "Site Activation Process" is centered in white. Below the text is a stylized landscape with green rolling hills and a thin purple line representing a horizon or path.

Microbicide Trials Network (MTN) Site Activation Process

What is site activation?

Process of completing key pre-implementation activities before receiving approval to initiate any MTN study



Who determines site activation requirements?

- Division of AIDS (DAIDS)
- Statistical and Data Management Center (SDMC-SCHARP)
- Network Laboratory (NL)
- Behavioral Research Working Group (BRWG)
- Coordinating and Operations Center (CORE)
 - FHI 360
 - University of Pittsburgh (PITT)

[Refer to Section 11 - Manual of Operational Procedures](#)



In consultation with the Behavioral Research Working Group (BRWG), the Statistical and Data Management Center (SDMC), the Network Laboratory (NL), and the U.S. National Institute for Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS), the Coordinating and Operations Center (CORE [FHI 360]) adapts specific requirements into a study-specific activation checklist for each study.

Snapshot of Activation Checklist

MTN-017

Phase 2 Randomized Sequence Open Label Expanded Safety and Acceptability Study of Oral Emtricitabine/Tenofovir Disoproxil Fumarate
Tablet and Rectally-Applied Tenofovir Reduced-Glycerin 1% Gel

Site Name and Location:

DAIDS Site Number:

Site Investigator of Record:

Study Activation Requirement	Approval Date	Comments
Preparatory Activities		
1. DAIDS-OCSSO MTN site approval (if applicable)		
2. Local regulatory authority (IRB/EC) submission/approval		
3. Protocol registration approval notice received from the DAIDS RSC Protocol Registration Office		
Pharmacy Requirements		
4. Adequate pharmacy staffing in place for study implementation		
5. Pharmacy Establishment Plan (PEP) approval by DAIDS or MTN Director of Pharmacy Affairs		
6. Completion of pharmacy staff training as deemed required by CORE (PITT) Pharmacist		
7. Approved standard operating procedures (SOP) for investigational study product management and Chain of Custody		
8. Import approval obtained for investigational study products (if applicable)		
9. Product availability on site		
10. MTN Director of Pharmacy Affairs approval of pharmacy readiness		
Data Requirements		
11. Availability of SDMC-provided study-specific materials on site		
12. Proper set-up of required DataFax data transfer equipment		
13. SDMC confirmation of successful receipt of CASI test data		

All sites will receive the study activation checklist once Version 1.0 of the protocol is approved and distributed to sites.

Upon receipt of the study activation checklist, sites need to maintain close communication with the management team for each of the activation requirements and FHI 360 will send regular updates (e.g. weekly) to sites about the status of activation as items are completed/accomplished.

Regulatory Approvals

Preparatory Activation Requirements

- DAIDS-OCSO Approval
- Local Regulatory Approval
 - Institutional Review Boards/Ethics Committees
 - Regulatory Entities
- DAIDS Protocol Registration Office (PRO) Initial Registration Notification

All sites must meet the DAIDS requirements and be approved as a Microbicide Treatment Network (MTN) Protocol Specific Site for participation in MTN 017. If the site has never participated in an MTN clinical trial before, it is considered new to MTN and must receive DAIDS Office of Clinical Site Oversight (OCSO) approval in addition to study-specific activation approval. The two processes may proceed simultaneously, but site approval must be granted prior to study-activation approval. Also, a new site cannot complete protocol registration until it has received OCSO site approval.

All required approvals by all responsible Institutional Review Boards/Ethics Committees (IRBs/ECs) must be obtained and documented prior to study initiation.

After obtaining approval from all responsible IRBs/Ecs/REs, sites must complete Protocol Registration procedures with the DAIDS PRO, which is part of the DAIDS RSC. Protocol Registration is completed for each MTN study on a site-by-site basis. The purpose of these procedures is for DAIDS to confirm regulatory compliance and completeness of site-specific ICFs and IRB/EC approval documentation prior to study initiation.

Local Regulatory Approval

IRB Submission Package

Protocol, **Informed Consent Forms (ICFs)**, Education/Recruitment Materials, Other Materials Required by IRB (informed consent support materials, case report forms and CASI/SMS/Interview scripts)

Informed Consent Forms (ICFs)



- Adapt Template (provided with protocol)
- Incorporate Site Specific Information (e.g. amount of reimbursement, length of study visit, contact information)
- Submit English Version to FHI 360 for Review
- Modify/Finalize English Version based on FHI 360 Recommendations
- Translate English Version (if applicable)
- Submit Translation/Back-Translation to FHI 360 for Review (if applicable)

Following the release of protocol version 1.0, FHI 360 will provide all sites with written guidance related to adapting site specific ICFs.

The CORE (FHI 360) will distribute copies of the sample ICFs as Microsoft Word documents to facilitate site-specific language changes. Site staff will adapt the sample ICFs into site-specific versions that reflect local procedures and IRB/EC requirements, site-specific information (for example, amount of participant reimbursement in local currency and local contact information.)

Study sites that will conduct the informed-consent process only in English will prepare English-language ICFs. Sites that will conduct the informed-consent process in local languages other than English will prepare English-language ICFs, local language ICFs (translated from the English version) and back-translated ICFs. Translations into local languages need not be completed by a certified translator; however, it is recommended that two different individuals translate the ICFs and then combine their work to prepare a composite. Back-translations from the local language ICFs into English should be completed by an individual who did not participate in preparing the local language ICFs.

The CORE (FHI 360) generally will provide review comments to site staff within three to five working days of receipt of the consent forms; however, the exact time for return of comments will depend on the number of ICFs to be reviewed and the

number of sites submitting ICFs.

Site staff incorporate review comments from the CORE (FHI 360) into the English ICFs and obtain translations and back-translations of any corrections or additions. Next, site staff re-submit the forms to the CORE (FHI 360) and repeat this process until final approval of the ICFs is obtained. Note: Finalization of ICFs is a collaborative effort between site staff and the CORE (FHI 360). It may take several reviews before all forms are finalized and ready for IRB/EC submission.

Sites are allowed to add/modify information in their site-specific ICFs, relative to the sample forms, to explain study concepts or to comply with IRB/EC requirements. If a site deletes or makes any substantive change to basic content (e.g. risk or alternative-treatment information) as presented in the DAIDS-approved sample informed consent form, the IoR or designee must provide written documentation to explain the deletions/change(s) at the time of registration submission to the DAIDS PRO.

Further guidance in MTN MOP section 11.2

PRO Initial Registration Notification

- IRB/EC & Regulatory Authority Approval Letters
- IRB/EC Approved Informed Consent Forms (ICFs)
- FDA Form 1572 (Statement of Investigator)
- Investigator of Record Curriculum Vitae (CV)

<http://rsc.tech-res.com/protocolregistration>



Upon obtaining all required IRB/EC approvals, site staff will submit required documents to the PRO per the guidelines in the DAIDS Protocol Registration Policy and Procedures Manual. All submissions are required to be submitted electronically via the DAIDS Protocol Registration System (DPRS).

Upon request, the CORE (FHI 360) may review documents and/or provide other assistance to site staff in completing the protocol registration process.

Protocol registration approval is not required prior to scheduling training; but if regulatory approval is not obtained before training occurs, the training may be postponed.

Once complete, each site may receive a final notification from the DAIDS PRO indicating that they have successfully completed the protocol registration process.



Site Activation Implementation Requirements

Implementation Requirements

- Operational
- Pharmacy
- Data Management
- Laboratory
- Behavioral
- Other (e.g. training, standard operating procedures, etc.)



Several pre-implementation steps must be completed before a study can be initiated. Several of these steps require collaborative work among Protocol Team and site-study staff members.
training.

Operational Considerations and Activities

- Establish Study-Specific Organizational and Staffing Plan
 - Determine staffing needs to ensure adequate staffing are in place for implementation
 - Determine clinic facility adequacy and needs
 - Study Staff Roster/Delegation of Duties*
- Site-Specific Visit/Flow Sheets/Vital Signs Flow Sheets
- Community Education Work Plan

*A reasonably complete study staff roster, signature sheet, and delegation of duties must be in place before training; a final version required before activation.

All designated staff must be adequately trained; CVs, training records, certifications, etc. must be properly stored in essential files.

Things to think about:

- Determine if space is adequate for study implementation
- Obtain all necessary furniture, if needed
- Designate specific areas where study activities will take place (i.e. randomization, storage of study supplies)
- Verify that all necessary equipment and supplies are available. If needed, obtain supplies and equipment
- Determine staffing needs based on study required procedures
- Hire additional staff, if needed, and provide required trainings

The CORE (FHI 360) Community Program staff work closely with CRS community staff to develop local community-involvement work plan (CIWP) that include community assessment, community education, and support of CABs and other mechanisms for community input.

Pharmacy Requirements

- Pharmacy Staffing
- Pharmacy Establishment Plan (PEP)
- Pharmacy Training
- Import Approvals (if applicable)
- Study Product Availability
- Male Condoms
- Lubricant

The above items listed must be in place before the MTN Director of Pharmacy Affairs approves the site for pharmacy readiness.

- Sites should have at least one dedicated PoR and one back up pharmacist in place.
- The MTN Director of Pharmacy will confirm if an approved DAIDS PAB PEP will be acceptable. If sites do not have a DAIDS PAB approved plan, the MTN Director of Pharmacy Affairs will provide template.
- Pharmacy training will likely be completed in conjunction with study specific training.
- The MTN Director of Pharmacy will provide sites with an MTN-017 Pharmacy Manual which includes instructions for ordering and dispensing study product and maintaining accountability records.
- Site pharmacists are required to provide/develop site-specific SOPs for to outline procedures for managing study product and chain of custody.
- MTN Director of Pharmacy Affairs will work with each site to confirm and prepare required documentation for submission and approval to local regulatory authority as applicable.
- MTN Director of Pharmacy Affairs will work with Gilead and CONRAD to ensure timely shipment and availability of gel and tablet in advance of study implementation.

Data Management Requirements

- Implementation Materials
 - Randomization Materials (envelopes, prescriptions, etc.)
 - Case Report Forms (CRFs)
 - Specimen Labels (PTID labels)
 - Other Tools (Visit calendar)
- DataFax Installation, including Testing, Confirmation

The above items listed must be in place before SCHARP approves the site for data management readiness.

Sub-bullets: 1-4 are materials/tools SCHARP will provide sites with as we move closer to activation.

Things to consider: the establishment of a filing system for study files, including participant's file and essential documents, obtaining all the required and necessary supplies (e.g. binder, folders); developing any study implementation materials needed prior to study initiation (e.g., participant appointment cards).

Laboratory Requirements

- Training (e.g. GCLP, lab safety, IATA shipping)
- Laboratory Staffing
- Laboratory Storage
- LDMS
- Laboratory Supplies
- Lab-Specific SOPs
- Laboratory Certifications (if applicable)
- IQA/EQA/VQA (if applicable)
- Assay validations (if applicable)

NL's approval of local CRS laboratory readiness, including the requirements listed below, is part of the MTN site-specific requirements for study activation.

Site-specific requirements for study activation may include, but are not limited to, the following:

- NL approval of proficiency in HIV testing, including validation of algorithm
- QA/QC procedures at the site
- site-specific normal ranges
- appropriate validation for protocol-specified tests
- local laboratory back-up arrangements per current cross-network policy
- IATA specimen-shipping certification
- site SOP for local specimen handling and chain-of-custody maintenance related to primary study endpoints
- use of LDMS
- CLIA certificates

The NL notifies the CORE (FHI 360) for the study when the site's laboratory-related procedures, facilities, and staff are deemed ready for study activation.

Note: GCLP/Safety training-Not Applicable to laboratory testing performed under CLIA certification.

Behavioral Requirements

- Training
 - Web-Based Computer-Assisted Self-Interview (CASI)
 - Short Message Service (SMS) Diary
 - Data Convergence Interview
 - Participant-Centered Adherence Counseling
- Systems Testing
 - CASI
 - Successful upload of test data in all languages
 - Confirmation of working back-up/mirror server
 - SMS
 - Successful transmission of test data

Counselors will receive training on completing the Data Convergence Interview and Participant Centered Adherence Counseling. They will complete mock interview sessions and will be audio-recorded once the study starts to ensure consistency of style among counselors. CASI will be web-based, and research staff will be trained on accessing the CASI and data entry. Sites should also have a mirror server or backup system in place if they anticipate that internet connection might be occasionally lost or slow, and should test data transmission using this server. Research staff will be trained on using the SMS system and will test data entry and transmission to ensure they are working properly from each site.



Site Specific
Standard Operating Procedures
(SOPs)

Standard Operating Procedures (SOPs)

- Describe the site's operational approach to conducting a particular study
- Serve to ensure standard, uniform performance of site- and study-related tasks
- Identify the individuals responsible for specific tasks
- Describe actions to be conducted by those responsible for specific tasks



Each site is expected to have written SOPs for site and study operations to ensure compliance with MTN and DAIDS policies and procedures, guidelines for Good Clinical Practice (GCP), and FDA regulations, where applicable.

- SOPs describe and document a site's approach to conducting research and serve to ensure standard, uniform performance of site- and study-related tasks. They identify the individuals responsible for specific tasks and describe actions to be conducted by those responsible. They may also serve as useful training tools for new staff.

Well-developed drafts of required site specific SOPs must be in place prior to study specific training; final versions are required before activation.

Well-developed drafts of all required study-specific SOPs must be submitted to designated reviewers, such as the CORE (FHI 360), SDMC Project Manager (PM), NL designee, the MTN Director of Pharmacy Affairs. **All required SOPs must be finalized and approved by the designated reviewer as a condition for site-specific study activation.**



Operational SOPs

- Communication with Responsible IRBs/ECs
- Participant Accrual
- Obtaining Informed Consent
- Participant Eligibility Determination
- Prevention of Participant Co-Enrollment
- Participant Random Assignment
- Participant Retention

Site SOPs describe procedures for general site operations that are applicable across all studies conducted at the site.

Study-specific SOPs describe the requirements and operations of a particular study.

If an established institutional site SOP adequately covers required procedures for individual studies, these may be used to fulfill study-activation SOP requirements. Certain SOPs should be study specific and reflect specific MTN-017 protocol requirements.

Safety Assessment & Reporting SOPs

- Participant Adverse Event Reporting
- Participant Safety Monitoring
- Clinical Management of Active Rectal or Reproductive Tract Infections (RTIs) requiring Treatment or Symptomatic Urinary Tract Infections (UTIs)

Note: Sites can opt to incorporate procedures for clinically managing active anorectal STIs, RTI, and UTIs into the safety monitoring SOP.

Protocol Implementation & Counseling SOPs

- HIV Counseling and Testing and Support/Referral Services for Participants found to be HIV-infected

Regulatory & Data Collection SOPs

- Data Management
- Source Documentation

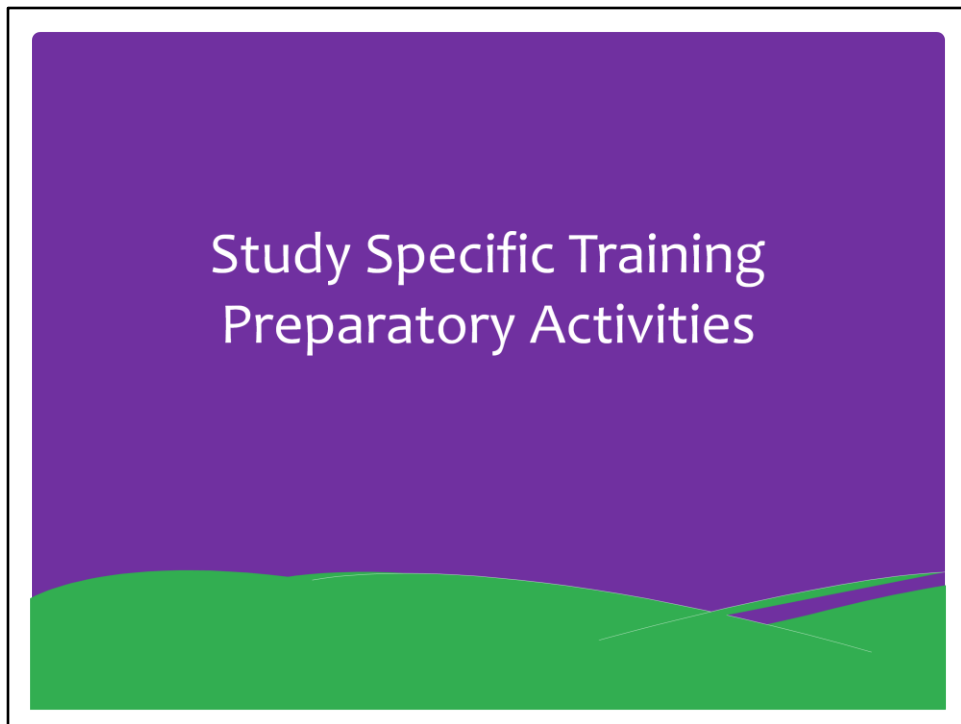
Data Management SOP should include site data management and QC/QA procedures and “the basics” of how study data will be collected and managed and what the day-to-day oversight of staff involved in data collection and management will be.

Things to think about:

- Establishment of a filing system for study files, including participant’s file and essential documents
- Obtaining all necessary supplies (e.g. binder, folders)
- Developing any study implementation materials needed prior to study initiation (e.g., appointment cards)

Pharmacy & Laboratory SOPs

- Pharmacy
 - Chain of Custody (e.g. facilities, administration, etc.)
- Laboratory
 - Specimen Acquisition, Processing, Tracking, Storage and/or Shipping



The MTN Director of Pharmacy Affairs and staff from the CORE (FHI 360), SDMC, NL, and other CORE (PITT) and DAIDS personnel collaborate with the IoR to fulfill this responsibility by conducting study-specific training.

Typically, study-specific training consists of a two- to five-day workshop conducted on site at each participating study site by participating members of the training team. During study-specific training, site staff and the training team examine and discuss in detail the study protocol, regulatory requirements, procedural requirements, and data collection specifications.

Training is conducted as close as possible to study initiation at each site to maximize effectiveness in preparing site staff to conduct each study. To achieve this goal, each site must complete certain study-activation requirements prior to study-specific training.

Site staff must conduct other activities to prepare for study-specific training and for conducting the study including

- hiring the necessary staff (if needed)
- designating staff members' study-specific roles and responsibilities
- assessing local training needs
- providing orientation and background training as needed, including on
 - local staffing and organizational plan (including roles and responsibilities)

- local site operations and SOPs
- local role-specific training/certification
- other local requirements
- reviewing and becoming thoroughly familiar with the study protocol, informed-consent forms, case-report forms, training materials, and other study implementation materials
- discussing and developing study-specific SOPs and other study-implementation plans and materials

Regulatory Training Requirements

- Human subjects protection (HSP)
- Good Clinical Practice (GCP)
- Essential Documents
- Source Documentation



<http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinicalSite.aspx>

Prior to the initiation of any MTN study, all personnel assigned to the study must complete training on the core set of site and study specific SOPs that are relevant to their study roles and responsibilities.

In addition to study specific training, site staff have to be fully qualified and trained staff to conduct such studies. These additional training requirements include human-subject protection (HSP), good clinical practices (GCP), and responsible conduct of research to DAIDS-sponsored clinical research sites.

Manual of Operational Procedures (MOP)

- Reference document for current MTN policies and procedures
- Does not replace the study-specific procedures (SSP) manual

MTN structure; operating policies; Roles and responsibilities of entities and individuals within the MTN; Protocol development and approval processes; Standardized study operations procedures; Data and specimen collection and processing procedures; Quality management, monitoring and evaluation of trials.

This manual provides general guidelines to all MTN sites and studies and combines MTN policies and procedures into one document.

All study procedures within the MTN must be conducted in accordance with the study protocol, the SSP manual, and this MOP.

In the event that there are inconsistencies between these documents, the precedence that must be followed is:

- If the MOP is inconsistent with the SSP, the SSP must be followed.
- If the SSP is inconsistent with the study protocol, the protocol must be followed.

Please inform FHI 360 immediately of any inconsistencies.

Become familiar with ...

- Study Protocol
- Study-Specific Procedures (SSP) Manual
- Implementation Tools
- Case Report Forms (CRFs)
- Informed Consent Support Materials
- MTN Manual of Operational Procedures (MOP)



Importance: to ensure understanding of the protocol, SSP, specifically background, rational for the study, study products and its side effects, and study procedures.

The SSP contains detailed guidance on study implementation. In addition to a study's protocol, the conduct of an MTN study is typically guided by an SSP manual. The SSP manual is an instructional and reference resource developed for each study that provides detailed standardized instructions for conducting protocol-specified procedures.

The development of the SSP Manual proceeds in parallel with CRF development, beginning when a protocol is nearly finalized. The CORE (FHI 360) CRM is responsible for assembling the manual in close cooperation with the SDMC PM, NL designee, and other key Protocol Team members.

Become familiar with ...

- HIV Risk Reduction Counseling
- HIV Pre/Post Test Counseling
- Protocol Adherence Counseling
- Product Use Adherence Counseling

Importance: to ensure understanding of the protocol and what the basic counseling requirements are for providing HIV and risk reduction counseling, protocol adherence and product use adherence as well as associated flow diagrams and procedures including HIV testing algorithms and counseling checklists.

Site staff should review the procedures/guidance outlined in the protocol to ensure participants are provided adherence counseling in accordance with standard participant-centered strategies and methods. It is important that discussions with participants are focused their experiences and identifying factors that would facilitate the ease/comfort of product use.

Site staff should also make sure they understand the importance of counseling the participant against product sharing.

Participants should be made to feel that there is no judgment when engaging with site staff. They should be afforded with a supportive environment where they are assured they can discuss their experiences using the products while fully understanding the decision to use the products and even participate in the study is their decision they are free to make.

Become familiar with...

- Physical and Rectal Examination Procedures
- Hepatitis B Vaccination
- STI/RTI Management
- Specimen Collection and Testing Procedures
- HIV Testing Procedures
- PK Specimen Collection Procedures



Site staff should review and discuss how clinical assessments (e.g. physical and rectal exams) are to be performed in accordance with the protocol. Determine how the Hep B vaccine will be administered. Determine how STIs be clinically managed, treated or how will referral for treatment be managed.

Site staff should become familiar Rectal Grading Table for Use in Microbicide Studies and the DAIDS Toxicity Table.

Regulatory Activation Approval

- MTN PITT CORE Regulatory Approval
- DAIDS Prevention Sciences Program Microbicide Research Branch Approval



MTN MOP section 11.11

After a site has completed all study-activation requirements, the CORE (FHI 360) sends the completed activation checklist to the DAIDS PSP MRB Chief or designee along with a request for activation approval. Upon review and approval from DAIDS, the CORE (FHI 360) will send an MTN Site-Specific Study Activation Notice to the site. Upon receipt of this notification, the site may initiate the study.

Questions & Answers



DAIDS Policies and Standard Procedures Documents

- **Site Implementation and Operations**

- Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials
 - * Appendix 1 - Essential Documents Recordkeeping Requirements
- Protocol Registration Policy
 - * Appendix 1 - Protocol Registration Algorithm
 - * Appendix 2 - Protocol Registration Manual
- Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials
 - * Appendix 1 - Source Documentation Requirements
- Requirements for Manual of Operational Procedures (MOP)
 - * Appendix 1 - Required Site SOPs

DAIDS Funded and/or Sponsored Clinical Trials

DAIDS Policies and Standard Procedures Documents

- **Site Implementation and Operations, cont.**
 - Requirements for Clinical Quality Management Plans
 - * Appendix 1 - Sample Clinical Quality Management Plan (CQMP)
 - * Appendix 2 - Sample Clinical Quality Management Chart Review Tool
 - * Appendix 3 - Sample Clinical Quality Management Regulatory File Review Tool
 - * Appendix 4 - Sample Clinical Quality Management Summary of Activities Tool
 - * Appendix 5 - Sample Clinical Quality Management Plan Annual Summary Report

<http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Pages/ClinicalSite.aspx>

DAIDS Funded and/or Sponsored Clinical Trials

Contact Information

Study-specific questions related to proper implementation, data collection, and laboratory concerns for a study protocol...

- MTN Coordinating and Operations Center (CORE)
- Statistical and Data Management (SDMC)
- MTN Network Laboratory (NL)

MTN-017 Management Team
mtn017mgmt@mtnstopshiv.org

